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Importance of systemic inflammation and hematological indices in gastric cancer staging

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Abstract
Aim: In this study, we aimed to assess whether preoperative C-reactive protein (CRP), hematological parameters, and indices can predict the stage of patients with gastric cancer.
Material and Methods: Five hundred and thirty-six patients with gastric cancer (stages I–III) were enrolled as case series analyses in this study.
Results: Patients with adenocarcinoma were older, leukocyte and albumin levels were lower, and CRP values were higher than in signet ring cell carcinoma patients. There was a statistically significant difference between the two pathological subgroups in terms of gender and tumor stages. Platelet (PLT) and PLT/lymphocyte ratios were found to be high in the advanced stage TNM Classification of Malignant Tumors (TNM) stage 3A, 3B, and 3C. The incidence of adenocarcinoma was found to be higher in the early stage compared to the late stage.
Discussion: Preoperative high CRP, low leukocyte, and albumin levels in patients with gastric cancer may be an indicator to distinguish signet ring cell carcinoma from adenocarcinoma. The preoperative high platelet and PLT/lymphocyte ratio may be useful predictive factors for differentiating in patients with stage 1A, 1B, 2A, and 2B and stage 3A, 3B, and 3C in gastric cancer.

Keywords
Gastric Cancer, C-reactive Protein, Platelet, Lymphocyte, Platelet/Lymphocyte Ratio

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Introduction

Gastric cancer remains one of the most common deadly cancers worldwide. While it is seen especially in the elderly and men, according to GLOBOCAN 2018 data, it is considered the fifth most common type of cancer in the world [1]. Since the incidence of gastric cancer includes many risk factors, it varies in different geographic regions. These risk factors include dietary habits, lifestyle, genetic predisposition, family history, Helicobacter pylori infection, occupational exposure, and radiation [2].

Computed tomography and endoscopy procedures are among the most commonly used diagnostic methods. Although these methods are accepted as the gold standard in the diagnosis of gastric cancer and have high sensitivity and specificity, less invasive and high specificity markers are necessary [3].

Various biomarkers have been investigated in gastric cancer in the previous literature. These have mostly been investigated at the molecular level in body fluids such as the blood, urine, saliva, and gastric fluid. Inflammatory cells are the basic cells of the microenvironment of cancer cells. Recent studies have shown prognostic factors associated with systemic inflammation in many types of cancer, including gastric cancer [4-8].

The aim of the study is to evaluate whether preoperative albumin, C-reactive protein (CRP), hematological parameters and indices can predict the stage of gastric cancer patients. Neutrophil, lymphocyte, monocyte, platelet (PLT), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), neutrophil/monocyte ratio (NMR), aspartate transaminase (AST), C-reactive protein (CRP), albumin, CRP/albumin (CRP/Alb) ratio, AST/PLT, and neutrophil/Alb ratio as inflammation-based markers were evaluated from patient records [9-11].

Material and Methods

The study was approved by the Ethics Committee of the institution (date: 27/05/2020, number: 64298). All patients who underwent subtotal gastrectomy or total gastrectomy between 2010 and 2019 were evaluated for case series analyses in the study. In total, 1,200 patients were screened. All patients were included in the study, except for those whose medical records were significantly missing, who did not have CRP, AST, albumin, and CBC at the time of diagnosis, and who were not followed up. Consequently, 536 gastric cancer patients were evaluated retrospectively (Figure 1).

The pathologic specimens of all patients were compared. All patients who underwent surgery for benign pathology, such as leiomyoma, were excluded from the study. Tumors containing neuroendocrine tumors or showing neuroendocrine differentiation were excluded from the study. Patients receiving neoadjuvant chemotherapy, radiotherapy, or chemoradiotherapy were also excluded from the study. The patients were classified as gastric adenocarcinoma, signet ring cell carcinoma, and poorly cohesive gastric carcinoma according to pathologic reports.

The pathologies of the patients were examined and divided into the TNM Classification of Malignant Tumors (TNM) grouping according to tumor size, lymph node metastasis, and distant metastasis. Accordingly, a stage was classified according to the AJCC staging system (8). Albumin, AST, CRP, and complete blood count (CBC) were obtained from the patient's medical record. The hematological indices, such as NLR, PLR, and NMR, were calculated based on preoperative laboratory data using CBC test results.

Statistical Analysis

For statistical analyses, SPSS 20.0 was used. Continuous variables were tested for normal distribution using the Shapiro-Wilk test. Results for normally distributed continuous variables were expressed as means and standard deviations; categorical variables were expressed as numbers (percentages). Student's t test was used to compare mean values; p values < 0.05 were considered statistically significant.

Results

The baseline characteristics of all cancer patients are shown in Table 1. When comparing pathological subgroups, it was revealed that patients with adenocarcinoma were older, their leukocyte levels were lower, and CRP values were higher than in signet ring cell carcinoma patients (Table 2). In addition, there was a statistically significant difference between the two pathological subgroups concerning gender and tumor stages (Table 1). When all cancer patients were divided into two subgroups according to their stages, only PLT and PLT/lymphocyte ratios were found to be high in the advanced stage (TNM Stage 3A, 3B, and 3C); see Table 2. In addition, there was a statistically significant difference regarding the pathology status of patients in subgroups formed according to stages. The incidence of adenocarcinoma was found to be higher in the early stage compared to the late stage (Table 1). No correlation was found between inflammatory parameters and cancer type and stage. Comparison of biochemical and hematological parameters is shown in Table 3.

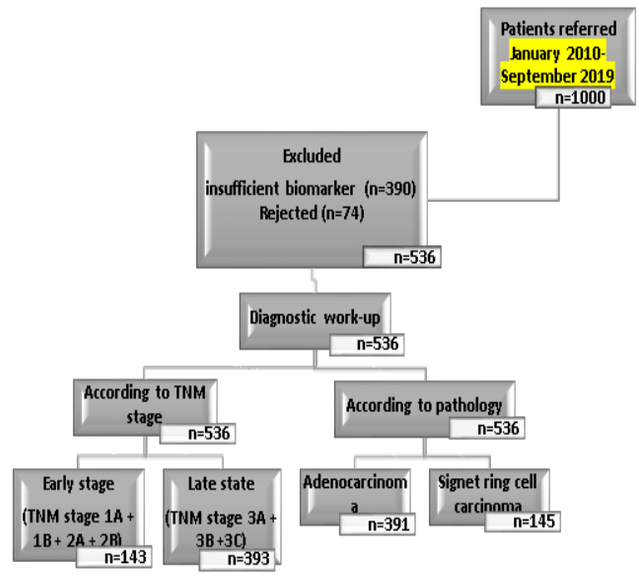

Figure 1. Study flow diagram

Table 1. Baseline characteristics of all cancer patients.

		N	Mean	Std. D.
Age		536	65.16	12.664
		Frequency (n)	Valid Percent (%)	
Gender	Female	174	32	
	Male	362	68	
Pathology	Adenocarcinoma	391	72.9	
	Poorly cohesive carcinoma	5	0.9	
	Signet ring cell carcinoma	140	26.1	
TNM	T1aN0	21	3.9	
	T1bN0	26	4.9	
	T1BN0	1	0.2	
	T1bN1	6	1.1	
	T1bN2	2	0.4	
	T1N0	3	0.6	
	T2aN0	1	0.2	
	T2N0	16	3.0	
	T2N1	14	2.6	
	T2N2	1	0.2	
	T2N3	2	0.4	
	T3aN3	1	0.2	
	T3bN0	1	0.2	
	T3N0	21	3.9	
	T3N2	14	2.6	
	T3N3	17	3.2	
	T3N3a	2	0.4	
	T4aN0	37	6.9	
	T4aN1	41	7.6	
	T4aN2	64	11.9	
	T4aN3	181	33.8	
	T4aN3a	3	0.6	
	T4aN3b	6	1.1	
	T4bN0	2	0.4	
	T4bN1	4	0.7	
	T4bN2	8	1.5	
	T4bN3	11	2.1	
	T4bN3a	1	0.2	
	T4N0	1	0.2	
	T4N1	4	0.7	
	T4N2	8	1.5	
	T4N3	8	1.5	
	T4N3a	4	0.7	
	T4N3b	4	0.7	
Stage	1A	51	9.5	
	1B	24	4.5	
	2A	39	7.3	
	2B	29	5.4	
	3A	32	6.0	
	3B	73	13.6	
	3C	288	53.7	

Table 2. Comparison of biochemical and hematological parameters in subgroups formed according to pathologies.

		N	Mean	Std. D.	p
Age (Year)	Signet ring cell carcinoma	145	58.75	12.33	0.00
	Adenocarcinoma	391	67.53	11.96	
Leukocyte (x109/L)	Signet ring cell carcinoma	145	8.25	3.29	0.01
	Adenocarcinoma	391	7.48	2.94	
Neutrophil (×109/L)	Signet ring cell carcinoma	67	4.84	1.87	0.36
	Adenocarcinoma	174	5.19	2.89	
C-reactive protein (CRP) (mg/L)	Signet ring cell carcinoma	85	8.36	17.64	0.01
	Adenocarcinoma	233	17.5	43.32	
Albumin (g/dL)	Signet ring cell carcinoma	70	4.21	1.32	0.01
	Adenocarcinoma	169	3.88	0.65	
Monocyte (x103/µL)	Signet ring cell carcinoma	62	0.57	0.21	0.71
	Adenocarcinoma	162	0.58	0.23	
Platelet (× 104/µL)	Signet ring cell carcinoma	124	263.35	80.91	0.18
	Adenocarcinoma	340	275.82	91.43	
Aspartate transaminase (AST) (U/L)	Signet ring cell carcinoma	145	20.63	16.47	0.84
	Adenocarcinoma	391	20.31	15.66	
Neutrophil / Lymphocyte	Signet ring cell carcinoma	145	4.8	6.86	0.57
	Adenocarcinoma	391	3.75	5.42	
PLT / Lymphocyte	Signet ring cell carcinoma	145	176.21	126.59	0.62
	Adenocarcinoma	391	181.77	109.63	
CRP / Albumin	Signet ring cell carcinoma	145	4.21	15.43	0.34
	Adenocarcinoma	391	5.69	16.20	
Neutrophil / Monocyte	Signet ring cell carcinoma	145	9.76	5.63	0.30
	Adenocarcinoma	391	9.18	5.84	
AST / Platelet	Signet ring cell carcinoma	145	0.11	0.35	0.23
	Adenocarcinoma	391	0.09	0.10	
Neutrophil / Albumin	Signet ring cell carcinoma	145	1.35	Oca.40	0.64
	Adenocarcinoma	391	1.40	1.2	

Discussion

Inflammation is a critical and fundamental process in the development and progression of cancer. In addition, the inflammatory response to cancer cells is associated with cancer progression. The inflammatory reaction is critical in the regeneration of tumor-damaged tissues and tumor microenvironment. Inflammatory cells are responsible for cell proliferation, angiogenesis, invasion, migration, and metastasis. Therefore, inflammation plays a vital role in cancer development and progression. Inflammation, malnutrition, and immune status are patient-related factors related to prognosis in gastric cancer patients.

Although difficulty with hemostasis has been described in gastric cancer patients, the precise association between albumin and CRP levels with adenocarcinoma and signet ring cell carcinoma has not been reported in a large-scale clinical study. However, the pathological mechanisms leading to distinctions in clinical and pathological features remain unclear [9]. In the current study, we demonstrated that patients with adenocarcinoma were older, leukocyte and albumin levels were lower, and CRP values were higher than in signet ring cell carcinoma patients. However, there was no significant disparity in the other parameters. Thus, low albumin and increased CRP levels could affect the tumor prognosis of patients with adenocarcinoma

Table 3. Comparison of biochemical and hematological parameters in subgroups formed according to the stage.

	Stage subgroups	N	Mean	Std. D.	p
Age (Year)	1A+1B+2A+2B	143	65.33	13.1	0.851
	3A+3B+3C	393	65.10	12.51	
Leukocyte (x109/L)	1A+1B+2A+2B	143	7.31	2.38	0.100
	3A+3B+3C	393	7.81	3.31	
Neutrophil (× 109/L)	1A+1B+2A+2B	74	4.62	1.80	0.065
	3A+3B+3C	167	5.30	2.93	
C-reactive protein (CRP) (mg/L)	1A+1B+2A+2B	97	14.4	39.82	0.831
	3A+3B+3C	221	15.3	37.78	
Albumin (g/dL)	1A+1B+2A+2B	70	4.5	0.68	0.379
	3A+3B+3C	169	3.94	0.99	
Monocyte (x103/µL)	1A+1B+2A+2B	68	0.55	0.17	0.196
	3A+3B+3C	156	0.59	0.24	
Platelet (× 104/µL)	1A+1B+2A+2B	130	248.68	72.19	0.000
	3A+3B+3C	334	281.76	92.98	
AST (U/L)	1A+1B+2A+2B	143	19.87	11.38	0.641
	3A+3B+3C	393	20.59	17.22	
Neutrophil / Lymphocyte	1A+1B+2A+2B	143	3.28	3.71	0.179
	3A+3B+3C	393	4.5	6.43	
PLT / Lymphocyte	1A+1B+2A+2B	143	162.23	102.15	0.027
	3A+3B+3C	393	186.83	117.94	
CRP / Albumin	1A+1B+2A+2B	143	5.54	16.99	0.827
	3A+3B+3C	393	5.20	15.64	
Neutrophil / Monocyte	1A+1B+2A+2B	143	8.93	4.96	0.318
	3A+3B+3C	393	9.49	6.5	
AST / Platelet	1A+1B+2A+2B	143	0.09	0.09	0.873
	3A+3B+3C	393	0.10	0.23	
Neutrophil / Albumin	1A+1B+2A+2B	143	1.24	0.73	0.071
	3A+3B+3C	393	1.44	1.25	

rather than signet ring cell carcinoma. The CRP, leukocyte, and albumin may be used to support clinical suspicions, follow the progress of the diagnosed disease, or facilitate the personalized treatment of patients. Particularly, CRP, leukocyte, and albumin levels may rise in well differentiated adenocarcinomas and signet ring cell carcinomas [10].

Serum CRP, an acute-phase protein, was shown to be a very sensitive prognosis indicator of inflammation in gastric cancer [10,11]. Low serum albumin levels as a negative acute-phase reactant have also been associated with gastric cancer patient survival and may hold promise as a prognostic predictor for such survival [12].

Li et al. identified differentially expressed microRNAs (miRNAs) among various gastric cancer subtypes in gastric cancer tissues [9]. Moreover, miRNA microarray analysis and bioinformatics analysis were used to compare miRNA expression between the signet ring cell carcinoma and tubular adenocarcinoma subtypes of gastric cancer. Lee et al. reported that the rate of lymph node metastasis and submucosal invasion in early gastric signet ring cell carcinoma was as low as those in early well-differentiated adenocarcinoma [13]. Endoscopic resection for early gastric signet ring cell carcinoma may be an alternative to surgical gastrectomy under certain conditions.

Poorly differentiated early gastric cancer has clinicopathologic features that are less favorable to endoscopic treatment than those of signet ring cell early gastric cancer. Therefore, these two types of early gastric cancer should be approached separately, not as a united type of undifferentiated histology, during the planning of endoscopic treatment. Chronic inflammation and associated high CRP levels play a role in cancer formation, and high CRP is not only a marker of cancer but is also associated with cancer formation [14,15].

It is important to differentiate early gastric cancers from advanced gastric cancers because most patients benefit from surgical treatment, and their lifespan dramatically varies from advanced stomach cancers. Studies continue to develop new biomarkers to predict the course of the disease in all cancer types. Therefore, in recent years, determining the course of cancer with cheap, simple, and objective markers in clinical practice has become a very important field of study in practice. In the current study, when all cancer patients were divided into two subgroups according to their stages, only PLT and PLT/lymphocyte ratio were found to be high in the advanced stage (TNM Stage 3A, 3B, and 3C). The incidence of adenocarcinoma was found to be higher at an early stage compared to a late stage. The PLT and PLT/lymphocyte ratio may play a role in an early stage (1A, 1B, 2A, and 2B) and late stage (3A, 3B, and 3C GC). However, statistical significance was not found in NLR. PLTs affect cancer progression, mostly by initiating and facilitating the development of inflammatory events. Platelets support tumor development, with many cytokines secreted. Interleukin (IL)-6 is one of the important cytokines whose serum concentration increases in the case of inflammation. IL-6 plays an important role in tumor progression in gastric cancer. It is well known that IL-6 stimulates carcinogenesis and metastasis through various signaling pathways [16]. IL-6, which stimulates the differentiation and proliferation of precursor cells in bone marrow, first directly affects megakaryocyte precursors by using special receptors.

According to Folman et al. [17], thrombopoietin and IL-6, two powerful stimulators of thrombocytosis, increase platelet count and products. This explains why cancers are usually accompanied by thrombocytosis. Neutrophils, platelets, and lymphocytes play crucial roles in tumor-related inflammation and immunology; therefore, their levels have prognostic value [18,19]. The clinical value of NLR or PLR as an independent predictor of gastric cancer prognosis is still controversial. Furthermore, few studies have focused on the relationship between stage-IV gastric cancer prognosis and NLR or PLR. Research regarding whether NLR or PLR can be used to stratify patients who would benefit from first-line chemotherapy is scarce [20]. Although NLR and PLR have previously been reported to predict cancer prognoses, to the best of our knowledge, our current study is the first to show the distinction between gastric cancer stages I–II and stage III with PLT, PLR, and NLR. Lee et al. [21] demonstrated that NLR, PLR, and changes in NLR or PLR are independent prognostic factors for overall survival in patients with advanced gastric cancer treated with chemotherapy. These specific factors may also help identify patients who are more sensitive to treatment regimen. NLR and PLR levels may be valuable indexes for lymph node metastasis [22]. NLR and PLR have diagnostic power and can discriminate patients with gastric cancer from patients without cancer [23]. In a meta-analysis,

increased PLR correlated with a higher risk of lymph node metastasis, serosal invasion, and advanced stage (III + IV) risk in gastric cancer. However, the PLR may not act as a negative predictor for the overall survival of gastric cancer [24]. Pan et al. suggest that the prognostic value of the Glasgow prognostic score (GPS) was comparable to the TNM stage, and both were superior to other inflammation-based prognostic scores (PLR, NLR) [25]. GPS score and TNM stage can be used together before surgery to provide a more appropriate prediction of survival and more reliable information on treatment decisions for patients with gastric cancer [25].

Some limitations exist in our study that are necessary to discuss. First, the sample size of this study: Since the slides and blocks of some patients could not be taken and evaluated again, they were excluded from the study. Our study was conducted within a signet center in central İstanbul. We could not evaluate other inflammatory parameters.

Conclusion

The combination of CRP, albumin, and leukocyte may effectively indicate the type of cancer, while the combination of PLT and PLT/lymphocyte ratio may effectively indicate the stage of cancer in gastric cancer patients. However, larger-scale, multicenter, and prospective studies, as well as different statistical studies and sample sizes showing the cancer type and stage of these parameters are needed. These results should be confirmed by prospective studies that include a larger number of patients and other prognostic factors.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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